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EORTC QLQ-C30 Summary Score reliably detects changes in QoL three months after anatomic lung resection for Non-Small Cell Lung Cancer (NSCLC).

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ABSTRACT

Introduction

We tested the European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) summary score (SumSC) to detect changes in the HRQOL after Non-small-cell lung cancer (NSCLC) surgery and compared its performance to the traditional scales.

Method

EORTC QLQ-C30 data was obtained from 326 consecutive pre-operative patients submitted for anatomical lung resections for NSCLC.66 patients completed post-operative assessments 3 months after surgery. The data was analysed to evaluate the ability of the SumSC compared to the traditional scales to (1) preoperatively differentiate between clinical groups; (2) detect post-op changes and to (3) compare pre and post-op changes in clinically different groups.The importance of perioperative changes was measured by calculating the effect size (ES).

Results

Of the 326 patients, those older than 70 years, with higher DLCO value and Performance Status (PS) ≤1 had a significantly better preoperative SumScore.

Physical function (PF) showed a large and significant decline (ES 0.91). Role and social function also showed a significant and medium decline (ES 0.62 and 0.41).

Postoperatively some symptoms scales showed significant increases in the values, implying worse symptoms with the largest increase in dyspnoea (ES -0.88). The change in General Health score (GH) was not significant after surgery (ES 0.26, p=0.062).

The SumSc, decreased significantly postoperatively. In particular, medium or large postoperative declines of SumSc were observed in both males and females, in patients with lower FEV1, lower performance score, and in those older than 70 years. Interestingly the decline of SumSc was observed irrespective of the preoperative DLCO level.

Discussion

The Summary Score was more sensitive to changes in subjects' HRQOL, than the GH score. The SumSc can be used as a parsimonious and easy to interpreted patient-reported-outcome measure in multi-institutional database and future clinical trials.

SUMMARY BOX

What is the key question?

- Can the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) summary score (SumSC) reliably detect changes in Health-Related (HRQOL) Quality of Life after Lung Cancer Surgery?

What is the bottom line?

- While our findings confirmed that HRQOL at the first post-surgical follow-up is worse compared the preoperative values in lung cancer patients, the Summary Score is more sensitive to changes in subjects' HRQOL, than the General Health Score.

Why read on?

- We confirmed that is feasible and reliable to use the EORTC QLQ-C30 summary score in a lung cancer surgical cohort. It will be a unique HRQOL index in clinical practice, to better inform patients about postoperative outcomes, and in clinical trial where it can be used as a parsimonious and easy to interpreted patient-reported-outcome measure.

1. INTRODUCTION

The impact of surgery on quality of life after surgical treatment for Non-Small Cell Lung cancer (NSCLC) is one of the most common concerns expressed by patients during the preoperative counselling(1). However, as demonstrated by a recent survey among members of the European Society of Thoracic Surgeons (ESTS), only few centres across Europe are routinely collecting these data during the perioperative period (2).

The perioperative fast-tracked management of lung cancer surgical candidates has streamlined the patient care but has reduced the time available for the patient to complete questionnaires. Surgical multi-institutional databases have been advocated to improve NSCLC care across countries and International Societies have agreed to standardize definitions and variables (3). Nevertheless, patient-reported outcomes (PROs) are still missing from these databases, leaving this evidence to small institutional studies. One reason for this paucity of data about PROs is the lack of recommendation on the instruments to use or the presence of multiple scores generated by each survey, each associated with several and different dimensions of Health-related-Quality-of-Life (HRQOL)

One important feature of a useful clinical database is the focus on a core set of standardized clinically relevant variables. Following this principle, the development of a single summary measure indicating an aggregate status of HRQOL is desirable.

Here, we tested the hypothesis that the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core30 (EORTC QLQ-C30) summary score (SumSC) is more sensitive to detect changes in the

HRQOL three months after lung cancer surgery compared to the traditional QLQ-C30 scales. The specific objectives were (1) to evaluate if SumSc at baseline differentiates between clinically distinct groups and how this compares with the traditional scoring; (2) to investigate if the SumSc is reliable in detecting post-op change, and how the performance compares with traditional scores; and eventually (3) to compare these changes in the clinically different groups.

2. MATERIALS AND METHODS

Prospective data collection was performed on a convenience sample of 326 patients who had undergone anatomic pulmonary resection for the treatment of lung cancer at the Leeds Cancer Centre, UK from April 2014 to September 2016 and had completed preoperative Health-Related Quality of Life assessment. 66 patients completed the questionnaire at three months after treatment.

The preoperative sample size number represents 47% of all patients operated for lung cancer during the same period in our unit. All the patients referred for histologically proven or with highly suspicion of lung cancer, were scheduled to be approached by our lung cancer specialist nurse during their preoperative appointments. As per NHS practice, all these patients are due to have a meeting with the lung specialist nurse prior surgery. The patients were asked to fill the baseline questionnaire in clinic and to give this back to the nurse or the doctor during the same appointment. Nevertheless, this was a service evaluation without a dedicated financial support and dedicated resource personnel. It relied on the voluntary work of a single lung cancer nurse specialist. When she was not available or engaged with another patient, other patients

were not approached and consented for the questionnaire. The response rate for the preoperative questionnaire was 98%. As no criteria were used to select patients for the preoperative questionnaire administration we believe the sample enrolled is representative of the entire cohort who received an operation for lung cancer during the same period.

The small proportion of patients filling the postoperative data is due first of all, to fact that only people living in the local Leeds metropolitan area received the follow-ups in the Leeds Cancer Centre whereas other patients were followed up in other satellite hospitals in the region. Furthermore, considering that this study relied on the crucial voluntary support of lung specialist nurse, we acknowledge that in the first Survivorship Clinic appointment, not all the nurses were aware of the study and able to give the questionnaire to the patients. As we reported a high completion rate in this follow-up time point (90%), the small number of postoperative questionnaires is due mostly to patients not approached.

To demonstrate the absence of possible selection bias, we run a comparison between the two groups. No statistical difference was noted in most of the clinical characteristics of all the patients completing the postoperative survey and those who completed only the baseline one.

Patients were selected for operation according to current functional guidelines and after discussion during a multidisciplinary tumour board meeting (4).

All patients were operated by consultants on the General Medical Council (GMC) specialist register in cardiothoracic surgery either through a muscle-sparing thoracotomy (n=62) or video-assisted thoracoscopic approach (VATS; n=265) depending upon the surgical indications (stage, size and location of the

tumour). All patients had a systematic mediastinal lymph node dissection along with the lung cancer resection.

Postoperative care followed standardized pathways of care and included as early as possible mobilization and oral food intake, intense chest physiotherapy and rehabilitation, deep venous thrombosis prophylaxis and chest pain control using a combination of patient-controlled analgesia and paravertebral infusion of local anaesthetic. The following baseline and surgical variables were screened for a possible association with HRQOL scores: age, sex, forced expiratory volume in 1 second (FEV1) expressed in percentage of predicted value, Eastern Cooperative Oncology Group performance score (PS), diffusing capacity of the lung for carbon monoxide (DLCO) expressed in percentage of predicted value. These variables have been associated with an increased risk of postoperative complications and consequently they are the most frequently factors investigated in lung cancer surgical patients (4-6).

The study was reviewed by the Research and Innovation Department of our hospital, which classified it as service evaluation and therefore did not need formal NHS Research Ethics Committee review.

2.1 Health-related-Quality-of-Life Assessment

QOL was assessed by administering in a clinic environment for self-completion. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Version 3, within 2 weeks before the operation and at 3 months after the operation. All the questionnaires were given

to the patients by the Lung Cancer specialist nurses during the standard-care appointments.

The EORTC QLQ-C30 is an internationally validated cancer-specific HRQOL questionnaire (7). The 30-item EORTC QLQ-C30 version 3.0 is composed by five multi-item function scales (physical [PF], role [RF], cognitive [CF], emotional [EF], and social [SF]), three multi-item symptom scales (fatigue [FA], nausea and vomiting [NV], and pain [PA]), six single-item symptom scales (dyspnea [DY], insomnia [SL], appetite loss [AP], constipation [CO], diarrhea [DI], and financial impact [FI]), and a two-item global quality of life scale (QL).

The questionnaire has a 1-week time frame and uses a four-point response format (‘‘not at all,’’ ‘‘a little,’’ ‘‘quite a bit,’’ and ‘‘very much’’), with the exception of the global QL scale, which are scored on a scale from 1 (very poor) to 7 (excellent).

The scores range from 0 to 100 after linear transformation of the raw scores. A high score for a functional scale represents a high level of functioning (healthier), whereas a high score for a symptom scale represents a high level of symptoms/problems.

2.3 Summary Score

Recently, the EORTC Quality of Life Group recommended the use of the QLQ-C30 summary score to supplement the 15-outcome profile generated by the QLQ-C30. The scoring algorithm for generating the QLQ-C30 summary score is available via the group’s Web site, http://groups.eortc.be/qol. The SumSc has been tested in a large existing dataset for validity and responsiveness to change over time. The EORTC Quality of Life Group steering Committee tested the SumSc comparing it to the individual QLQ-C30 scales using pre-treatment

QLQ-C30 data (N: 3,282) and conducting a confirmatory factor analysis. They also tested the seven HRQOL higher order measurement models evaluated by Gundy et al (8, 9). The use of a single score describing sensibly the HRQOL in clinical practice, will facilitate the routine collection of PROs and consequently their adoption in health-applied research. Preliminary data of a joint Society of Thoracic Surgeons (STS) and ESTS lung cancer surveillance survey, have shown as the HRQOL collection is still underrepresented across the two continents five years after surgery(10).

The SumSc is calculated from the mean of 13 of the 15 QLQ-C30 scores (the Global Quality of Life score and the Financial Impact score are excluded).

Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed (11, 12).

2.4 Statistical analysis

Descriptive analysis

All quality of life scores were calculated according to the scoring manual (11). The summary score was calculated according to Giesinger et al. (9), which led to a single score ranging from 0 (worst) to 100 (best). Descriptive statistics included counts and percentages, medians and inter-quartile ranges. Normality of distribution of numeric variables (including the QoL scores) was assessed by the Shapiro Wilk test.

Post-operative Change analysis

Before-after differences of QoL scales at 3 months were calculated using the Wilcoxon matched pairs rank-sum test. In addition, the importance of the perioperative changes in QoL scales was measured by calculating the effect size (mean change of the variable divided by its baseline standard deviation) (13, 14). Effect sizes of 0.2, 0.5 and 0.8 indicate a small, medium and large difference, respectively. The sign before the effect size indicates the direction of the difference (a positive sign means that the preoperative value is greater than the postoperative one). Between groups calculations made use of the independent t-test for numeric variables with normal distribution or of the Wilcoxon rank-sum test for those without normal distribution. Categorical variables were compared by using the Chi-square test or the Fisher's exact test (in case of 10 or fewer variables in at least one of the cells). All analyses were exploratory in nature, thus significant p-values ($p < 0.05$) should not be interpreted as confirming a priori hypothesis. The analysis was performed on Stata 12.0 statistical software (Stata Co., College Station, TX).

3. **RESULTS**

The characteristics of the 326 patients included in the study are shown in table 1.

Table 2 shows the comparison between the patients with both preoperative and postoperative HRQOL assessments and those who have completed only the preoperative questionnaire. In the group of patients who completed the postoperative questionnaire, we found 3-fold higher proportion of operations

performed through thoracotomy (p=0.008) and a greater proportion of females (p=0.002).

3.1 Baseline HRQOL and analysis of SumSc

Table 3 shows the preoperative values of the individual QoL scores.

The median preoperative SumSc in the entire population was 87.4 (IQR 77.2-93.6).

One hundred and forty-seven patients (45%) were older than 70 years of age. Compared to younger patients they had a higher (better) preoperative SumSc (90.6, IQR 79.9-94.9 vs. 85.3, IQR 74.0-92.5; p=0.003).

Twenty-four patients (7.4%) had a preoperative performance score (PS) assigned by clinicians, greater than 1 (2 or 3). The Eastern Cooperative Oncology Group (ECOG) Performance Score measures how the disease impacts a patient's daily living abilities rating this from 0 (fully active) to 5 (death)(15).

These patients had a worse preoperative SumSc compared to patients with performance score of 0 or 1 (74.7, IQR 57.7-92.2 vs. 87.8, IQR 77.8-94.0; p=0.004).

One hundred and fifty-three patients (46.9%) had a preoperative DLCO lower than 70% predicted value. These patients had a lower baseline SumSc compared to those with higher DLCO (85.7, IQR 74.9-92.1 vs. 89.7, IQR 79.8-94.6; p=0.019).

There were no differences of preoperative SumSc between male and female patients (89.7, IQR 75.8-94.0 vs. 86.5, IQR 77.4-93.5; p=0.38) or between

patients with FEV1 lower than 70% and those with higher FEV1 (86.4, IQR 76.3-93.6 vs. 87.6, IQR 77.2-93.6; p=0.62).

3.2 Perioperative Changes Analysis

Patients eligible for the postoperative assessment were those who were referred to the Leeds Survivorship Clinic which is including only patients coming from the Leeds metropolitan area and not needing additional postoperative therapies. Of those, sixty-six patients completed the EORTC QLQ C30 questionnaire three months after the operation (90% completion rate).

Table 4 shows the perioperative changes of QoL scales and SumSc in this population. PF showed a large and significant decline at three months. RF and SF showed a significant and medium decline (effect sizes 0.62 and 0.41, respectively) (effect size 0.91).

Some of the symptom scales (FA, PA, DY, FI) showed a postoperative significant increase in their values (worse symptoms). In particular, DY was the one with the largest increase (effect size -0.88).

The change in General Health score (GH) was not significant after surgery (effect size 0.26, p=0.062). At variance with the GH, the SumSc decreased significantly at three months (effect size 0.48, p<0.001). From a clinical point perspective, we are expecting a decrease in HRQOL especially during the first three months after operation(5).

3.3 Subgroups Analysis

Table 5 shows the perioperative changes of SumSc in different groups of patients with or without risk factors for surgery. Caution should be used when interpreting these results for the small numbers of patients in each subgroup.
In particular, medium or large postoperative declines of SumSc were observed in both males and females, in patients with lower FEV1, lower performance score, and in those older than 70 years of age. Finally, a similar postoperative medium decline of SumSc was observed irrespective of the DLCO level.

4. DISCUSSION

The Cardio-Thoracic speciality has been one of the first ones to introduce and champion the risk-adjusted outcome analysis for monitoring and improving quality of care (16, 17). However, there is an increasing interest in investigating the possible inclusion of the patient's perspective in these scores (18). The first step in this field is to identify the most appropriate indicator of the patients' voice: the SumSc can represent a valuable candidate for this, reflecting the patients' self-assessment of their daily life after a surgical operation for lung cancer.

4.1 Main findings

In our cohort of surgical lung cancer patients, HRQOL decreased three months after the operation. This decline varied through the scales with meaningful effects confirmed in the Social, Physical and Role Functioning and in the Dyspnoea symptom score. The General Health score, which reflects the

patient's consideration of their quality of life, did not change significantly between pre-and post-treatment.

Our results showed, on the other hand, that the EORTC Summary Score was significantly reduced after surgery.

We were also able to show that SumSc detected important differences between subgroups of patients confirming the existing evidence. The analysis of subgroups of patients considered clinically at high risk for surgery, although limited in numbers, showed interesting results confirming that objective variables cannot be considered as surrogates of patient-reported quality of life. For example, Gender and FEV1 were factors not associated with different preoperative QoL scores. Patients with lower DLCO, an age older than 70 years or a PS>1 reported lower baseline values of SumSc. However, as demonstrated in the past (6, 19), DLCO was not associated with a greater QoL decline according to the SumSc analysis.

4.2 Findings in the existing literature

The global domain of HRQOL is a concept of particular interest especially from the patient's point of view as this is the domain, which they are always referring during the surgical consultation. However, it must contain most of the components of the patient's life, correctly weighted.

Giesinger and colleagues have already shown that the validity and responsiveness of the EORTC QLQ-C30 SumSc is equal or even superior to the original underlying QLQ-C30 scales scores (9). Most recently, the SumSc has also demonstrated good ability to detect changes in subjects' quality of life among patients with unresectable hepatocellular carcinoma(20). Similar to our

result, the authors showed that the SumSc performed better than the Global Health scale of QLQ-C30 especially in showing changes over time.

Several investigations have described significantly reduction in HRQOL after surgical resection for lung cancer. This decrease is particular evident in the first postoperative period, to improve, although not completely to preoperative levels, in the following months (5, 21). The SumSc in our series confirmed this trend in conjunction with most of the single functioning and symptom scales, while the General Health score didn't.

Regarding the age-related sub analysis, several studies have demonstrated that age is not a major determinant of quality of life after lung resection for cancer. Ferguson and colleagues found no difference in the postoperative QOL scores between patients younger or older than 70 (6). Burfeind and colleagues used the EORTC QLQ-C30 instrument in a prospective, longitudinal study to assess their lobectomy patients and found no significant difference between older (>70 years) and younger cohorts (22).

The SumSc in our population, showed a large decline after three months from the operations only in patients older than 70 years, probably taking into consideration all the detailed aspects of the older patient's quality of life, which are not easily detected by answering to the generic question.

Our results show that the gender-specific analysis does not follow the trend previously described in thoracic oncology surgery, for example Chang et al. reported gender was a significant determinant of the HRQoL aspects of physical, emotional and cognitive functioning(23).

The SumSc in our series was largely reduced in patient with forced expiratory volume in the first second (FEV1) lower than 70% of predicted, although at the

baseline assessment there were no difference between these two groups. In our previous study of 220 patients investigated with the SF-36 questionnaire before and after surgery, we selected patients with chronic obstructive pulmonary disease (COPD) to compare their HRQOL with a case-matched population of patients with normal respiratory function. We were not able to find differences between the groups in any of the preoperative and postoperative physical and mental QoL scales(24). Ferguson and co-authors, using the EORTC QLQ-C30 and LC-13 module, found that FEV1 as a consistent predictor of physical function, role function, fatigue, pain, and dyspnoea. However, this cross-sectional study has a much longer follow-up of (2.7 year), whether our analysis was focused only on the very short-term (6).

In US the first attempt to incorporate PROs in the Society of Thoracic Surgeons database with the National Institutes of Health Patient Reported Outcome Measurement Information System (PROMIS) has demonstrated the feasibility of the future integration in lung cancer patients records(25). The American College of Chest Physicians (ACCP) has made the quality of life data collection a class 2B recommendation for all lung cancer surgery patients(26). We need now to overcome the difficulty of streamlining this collection in the daily practice, and to find the best standardized PROMs to be included in these already enormous clinical databases.

4.3 Limitations:

This study has some limitations.

- First of all, we collected a limited number of postoperative assessments. This is due to logistical reasons with only patients who live in the surrounding area being followed up in our Hospital, where the preoperative assessment has taken place. Furthermore, patients eligible for the first postoperative assessment were only patients who did not require postoperative chemotherapy or radiotherapy and were referred to Leeds Survivorship clinic. We cannot rule out that the inclusion of all the patients may affect our results. However, the characteristics of the patients who did not participate in the 3 months assessment were similar to those included in the analysis except for a lower proportion of VATS procedures and a predominance of female patients (Table 2).

-The results of this study showed a difference between perioperative changes detected by GHS and SumSc. Our interpretation of superiority of SumSc may be challenged by future studies comparing the EORTC SumSc with other corresponding summary scores derived from other types of questionnaires (revealing a type I error in our study). Unfortunately, we were not able to administer to the same patients more than one questionnaire. As already shown in previous investigations(27) the administration of multiple QoL questionnaires evaluating similar concepts or domains may be too time consuming and stressful for the patient and introduce other biases.

- Most of the operations were performed using VATS. The minor incidence of the post-thoracotomy pain especially in the early postoperative period has been recently reported in a large randomized trial comparing the two surgical approaches (28).

We acknowledge that it would be interesting to verify whether similar results would be found analysing a population with a larger proportion of thoracotomies.

- We included only anatomical lung resections in our analysis. Future investigations are needed to explore the use of a SumSc with different surgical operations for lung cancer as wedge resections or with stages requiring postoperative additional therapies.

-Finally, our study is limited to the three months follow-up. We have chosen this timeframe as this is when the major changes in HRQOL have been described and also to reduce the attrition rate. However, future investigations are warranted to evaluate the SumScore performance after three months from surgery.

4.4 Conclusions:

The Summary Score was more sensitive to changes in subjects' HRQOL, than the General Health Score. As suggested by the EORTC Quality of life group, the SumSc can avoid problems with potential type I errors that arise because of multiple testing when making comparisons based on the 15 outcomes generated by this questionnaire. In addition, the use of the QLQ-C30 summary score can reduce sample size requirements in clinical trials were HRQOL is a primary endpoint. In conclusion, our results suggest that the SumSc can be used as a parsimonious and easy to interpreted patient-reported-outcome measure in multi-institutional database and future clinical trials.

Contribution: Study concept and design: CP, AB, KF, MK, GV and KA. Acquisition, analysis or interpretation of data: CP, AB, AI, GV and MK. Drafting of the manuscript: CP. Critical revision of the manuscript for important intellectual content: all authors.

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